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(54) **DEVICES AND METHODS FOR LOCATING A SAMPLE READ IN A REFERENCE GENOME**

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(52) **U.S. Cl.**

CPC ***G16B 30/00*** (2019.02); ***G16B 30/10*** (2019.02); ***G16B 40/00*** (2019.02)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

A device for locating a sample read with respect to a reference genome includes a plurality of groups of cells. Each group of cells stores a reference sequence representing reference bases from the reference genome corresponding to an order of cells in the respective group of cells. Each group of cells further stores a current substring sequence representing sample bases from the sample read corresponding to the order of the cells in the respective group of cells. Each group of cells stores the same current substring sequence and a reference sequence representing a portion of the reference genome that partially overlaps at least one other portion of the reference genome represented by one or more other reference sequences stored in one or more other groups of cells. Groups of cells are identified among the plurality of groups of cells where the stored reference sequence matches the current substring sequence.

25 Claims, 8 Drawing Sheets

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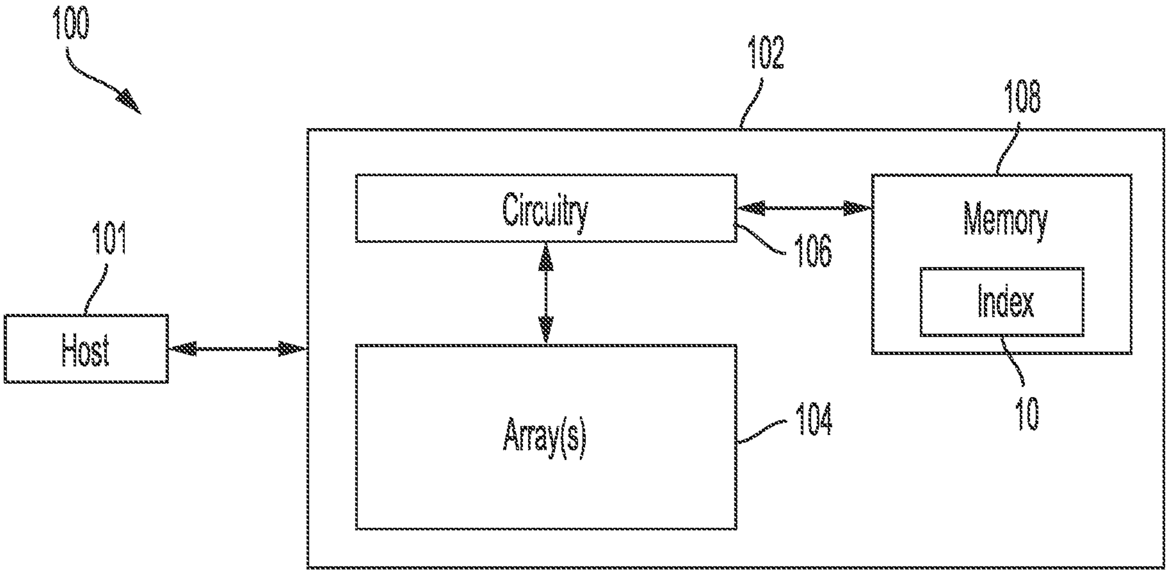
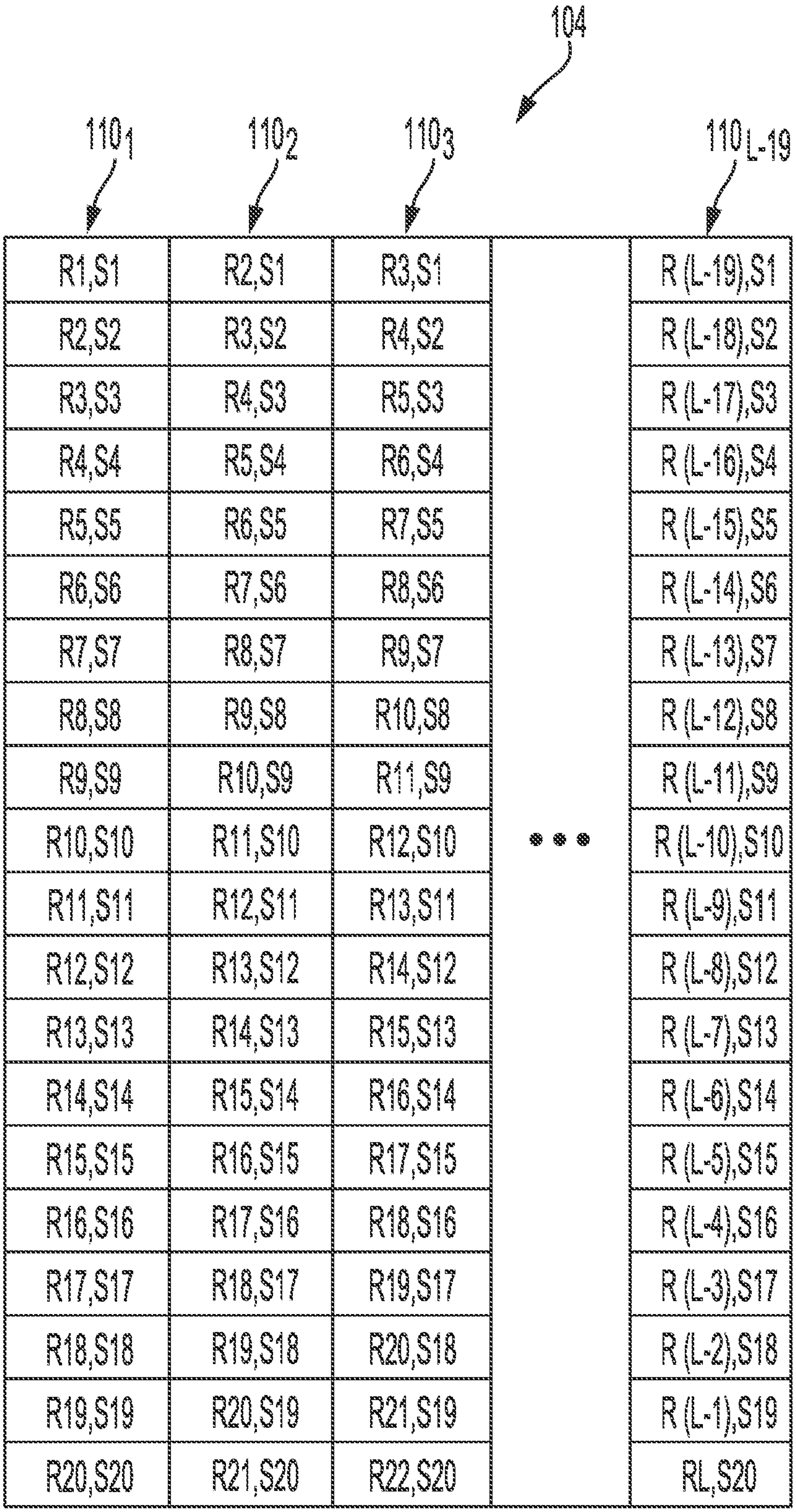

100
102
108
Circuitry
Memory
106
Index
101
Host
10
Array(s)
104

FIG. 1


104
110_1
110_2
110_3
110_{L-19}

R1,S1	R2,S1	R3,S1		R (L-19),S1
R2,S2	R3,S2	R4,S2		R (L-18),S2
R3,S3	R4,S3	R5,S3		R (L-17),S3
R4,S4	R5,S4	R6,S4		R (L-16),S4
R5,S5	R6,S5	R7,S5		R (L-15),S5
R6,S6	R7,S6	R8,S6		R (L-14),S6
R7,S7	R8,S7	R9,S7		R (L-13),S7
R8,S8	R9,S8	R10,S8		R (L-12),S8
R9,S9	R10,S9	R11,S9		R (L-11),S9
R10,S10	R11,S10	R12,S10	• • •	R (L-10),S10
R11,S11	R12,S11	R13,S11		R (L-9),S11
R12,S12	R13,S12	R14,S12		R (L-8),S12
R13,S13	R14,S13	R15,S13		R (L-7),S13
R14,S14	R15,S14	R16,S14		R (L-6),S14
R15,S15	R16,S15	R17,S15		R (L-5),S15
R16,S16	R17,S16	R18,S16		R (L-4),S16
R17,S17	R18,S17	R19,S17		R (L-3),S17
R18,S18	R19,S18	R20,S18		R (L-2),S18
R19,S19	R20,S19	R21,S19		R (L-1),S19
R20,S20	R21,S20	R22,S20		RL,S20

FIG. 2

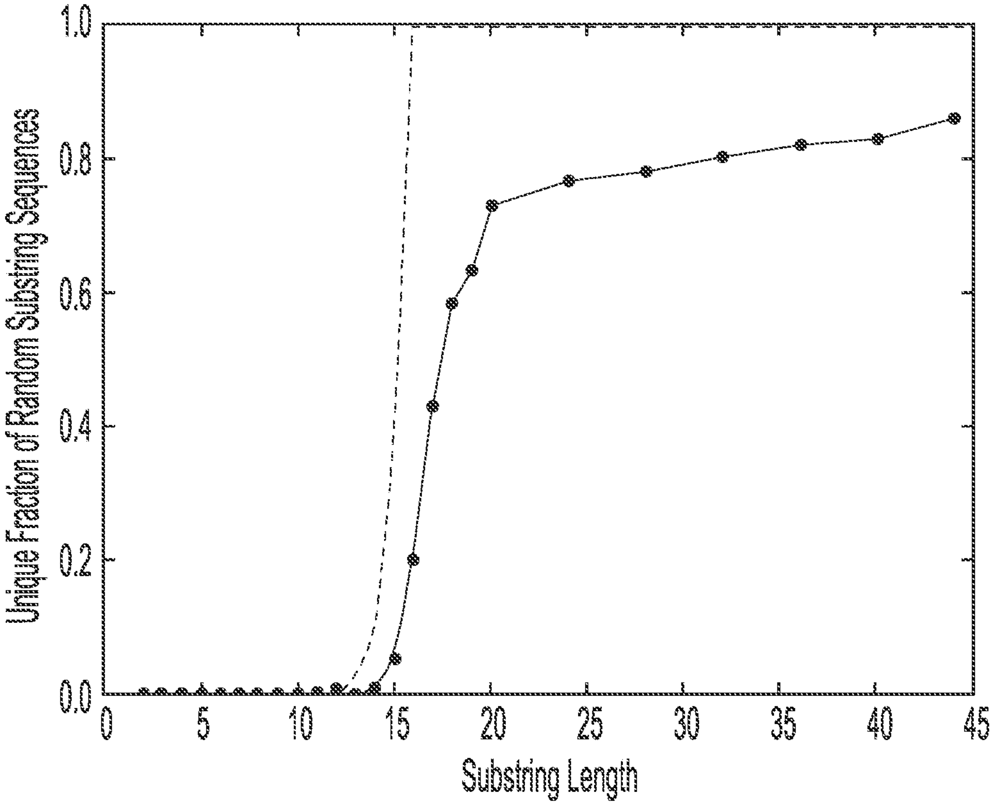

1.0
0.8
0.6
0.4
0.2
0.0
Unique Fraction of Random Substring Sequences
0
5
10
15
20
25
30
35
40
45
Substring Length

FIG. 3

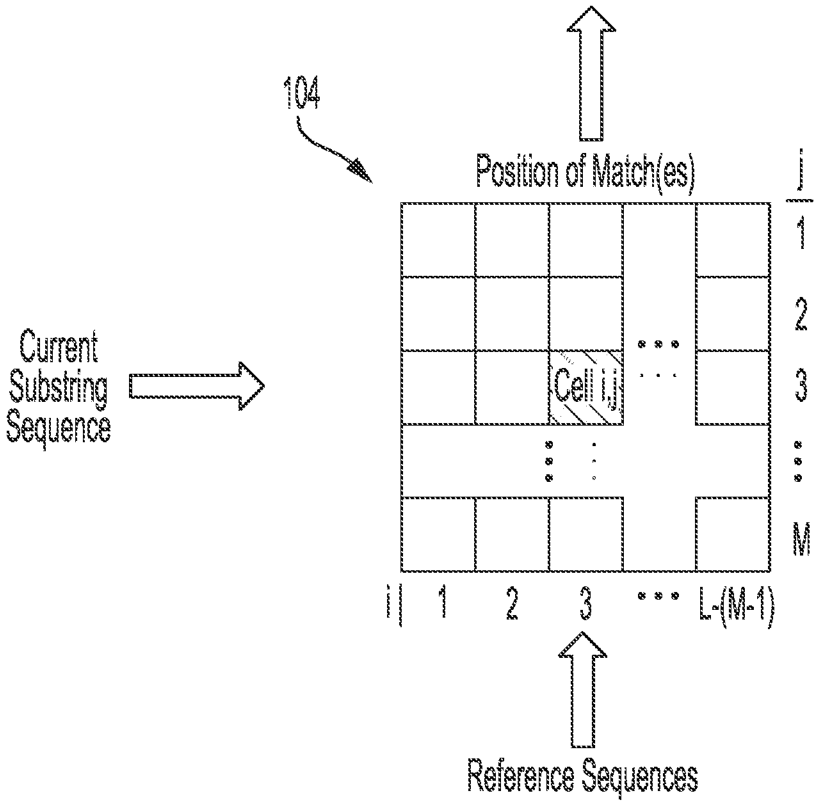

104
Position of Match(es)
j
1
2
3
⋮
M
Current
Substring
Sequence
Cell i,j
i
1
2
3
L-(M-1)
Reference Sequences

FIG. 4A

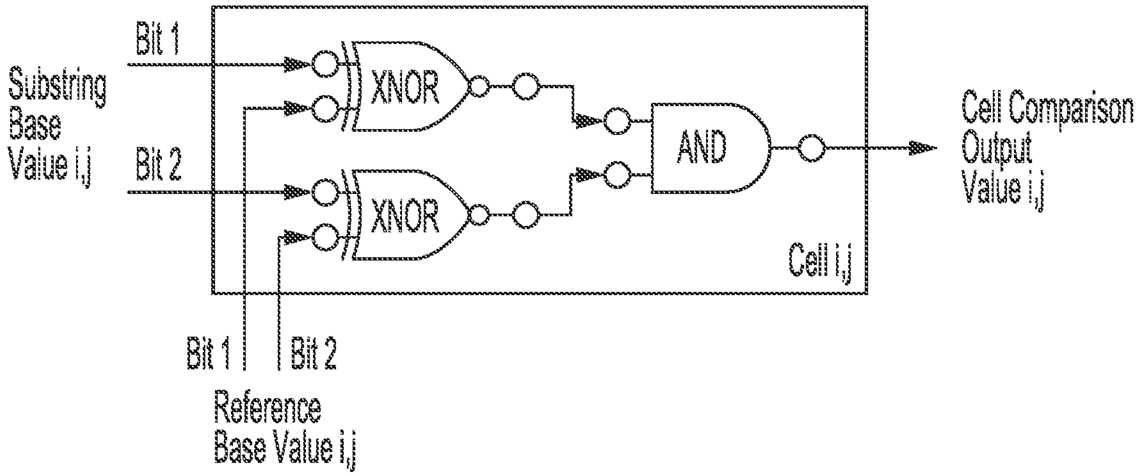

Bit 1
Substring
Base
Value i,j
Bit 2
XNOR
XNOR
AND
Cell Comparison
Output
Value i,j
Cell i,j
Bit 1
Bit 2
Reference
Base Value i,j

FIG. 4B

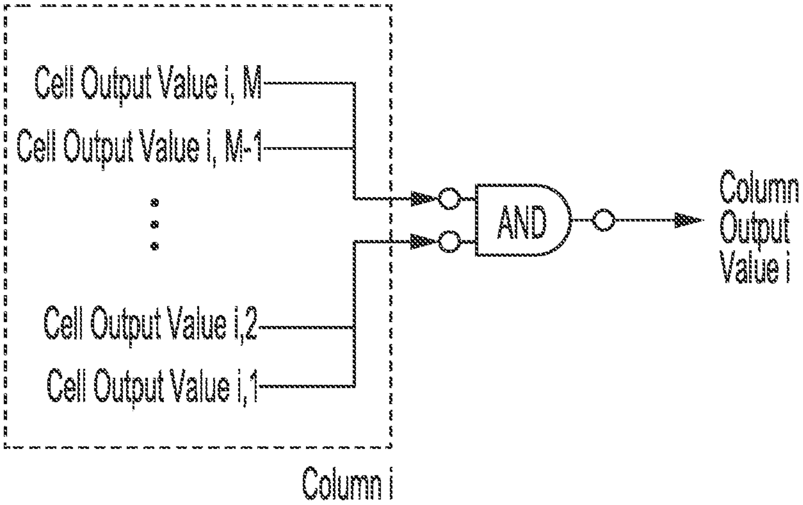

Cell Output Value i, M
Cell Output Value i, M-1
Cell Output Value i,2
Cell Output Value i,1
AND
Column Output Value i
Column i

FIG. 4C

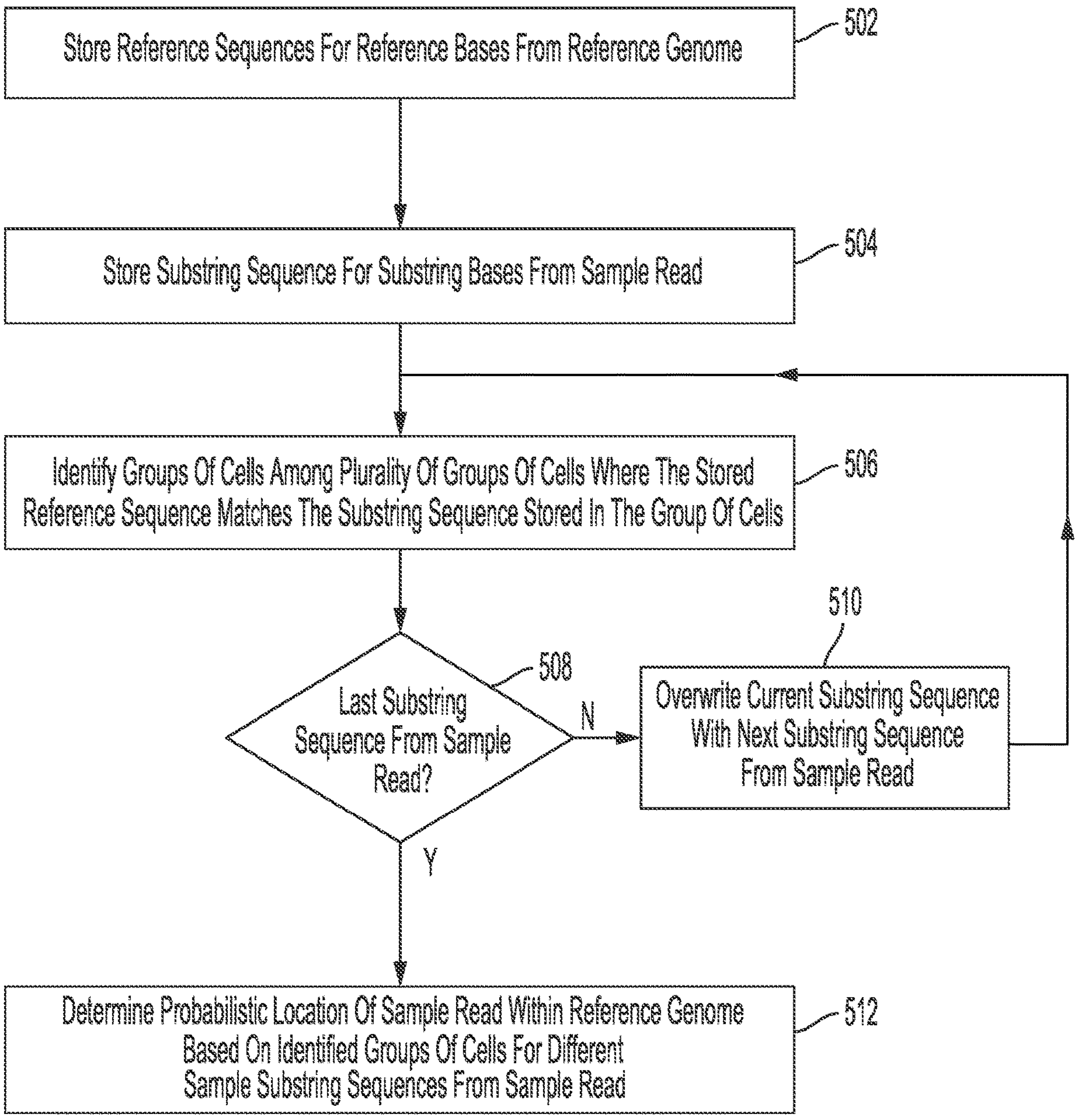

Store Reference Sequences For Reference Bases From Reference Genome
502
Store Substring Sequence For Substring Bases From Sample Read
504
Identify Groups Of Cells Among Plurality Of Groups Of Cells Where The Stored Reference Sequence Matches The Substring Sequence Stored In The Group Of Cells
506
Last Substring Sequence From Sample Read?
508
N
Overwrite Current Substring Sequence With Next Substring Sequence From Sample Read
510
Y
Determine Probabilistic Location Of Sample Read Within Reference Genome Based On Identified Groups Of Cells For Different Sample Substring Sequences From Sample Read
512

FIG. 5

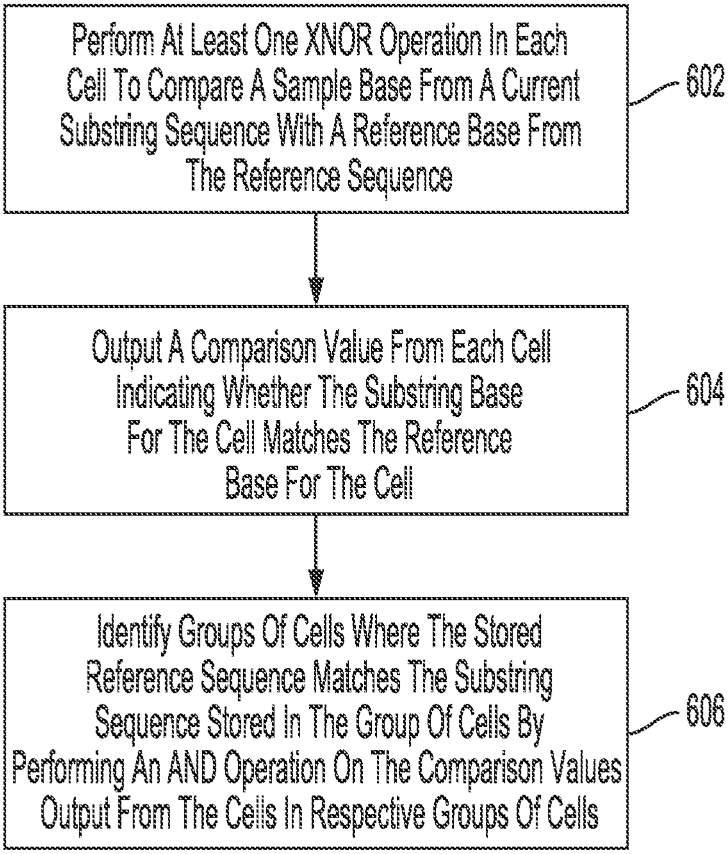

Perform At Least One XNOR Operation In Each Cell To Compare A Sample Base From A Current Substring Sequence With A Reference Base From The Reference Sequence
602
Output A Comparison Value From Each Cell Indicating Whether The Substring Base For The Cell Matches The Reference Base For The Cell
604
Identify Groups Of Cells Where The Stored Reference Sequence Matches The Substring Sequence Stored In The Group Of Cells By Performing An AND Operation On The Comparison Values Output From The Cells In Respective Groups Of Cells
606

FIG. 6

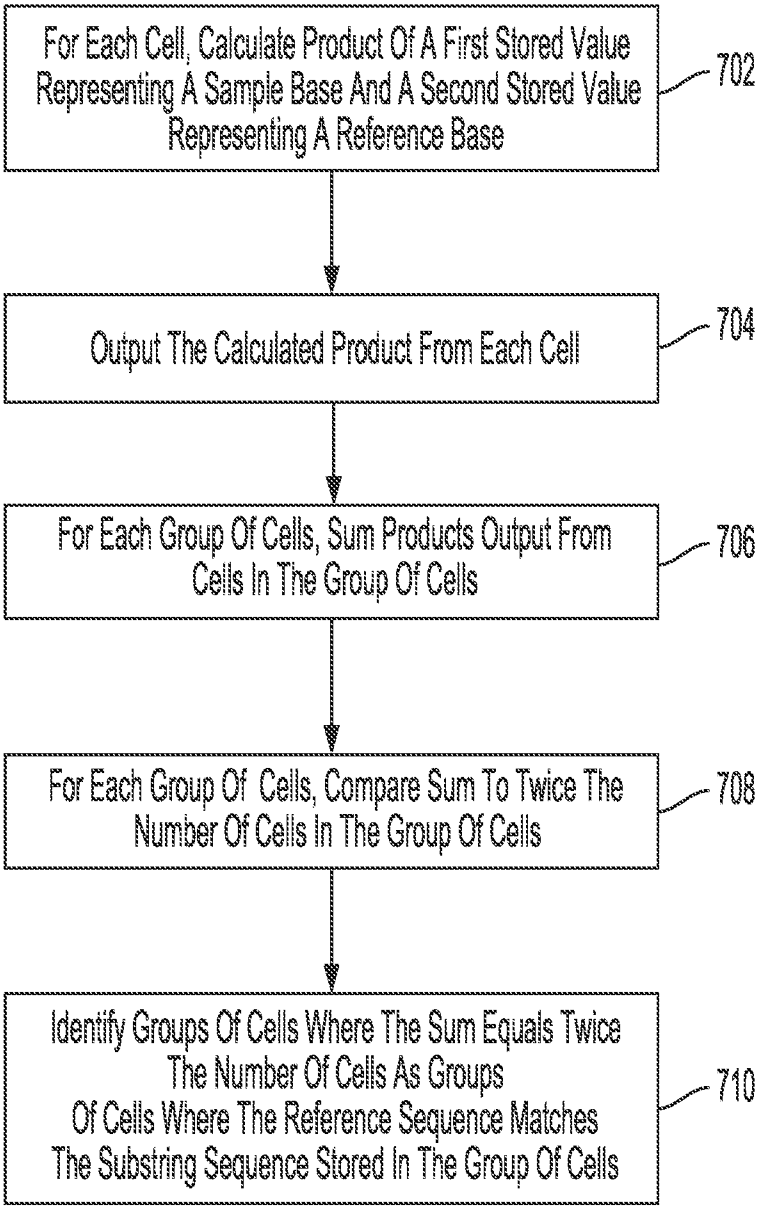

For Each Cell, Calculate Product Of A First Stored Value Representing A Sample Base And A Second Stored Value Representing A Reference Base
702
Output The Calculated Product From Each Cell
704
For Each Group Of Cells, Sum Products Output From Cells In The Group Of Cells
706
For Each Group Of Cells, Compare Sum To Twice The Number Of Cells In The Group Of Cells
708
Identify Groups Of Cells Where The Sum Equals Twice The Number Of Cells As Groups Of Cells Where The Reference Sequence Matches The Substring Sequence Stored In The Group Of Cells
710

FIG. 7

DEVICES AND METHODS FOR LOCATING A SAMPLE READ IN A REFERENCE GENOME

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is related to co-pending application Ser. No. 16/821,849, filed on Mar. 17, 2020, and entitled "REFERENCE-GUIDED GENOME SEQUENCING", the entire contents of which are hereby incorporated by reference. This application is also related to co-pending application Ser. No. 16,822,010, filed on Mar. 18, 2020, and entitled "REFERENCE-GUIDED GENOME SEQUENCING", the entire contents of which are hereby incorporated by reference.

BACKGROUND

Limitations in current DNA (deoxyribonucleic acid) sample handling lead to sample reads or portions of a sample genome having a generally unknown location in the sample genome. For de novo sequencing, which does not use a reference genome in comparing sample reads to each other to locate the sample reads within the sample genome, the sample reads are typically analyzed as a single large group, which requires significant memory resources and a high computational cost to compare the sample reads in the large group to one another to determine locations for the sample reads within the sample genome. Such conventional methods of de novo sequencing are not scalable relative to the large amount of data that needs to be processed for genome sequencing. In more detail, conventional methods of de novo sequencing usually store a large group of sample reads in a shared memory, such as an expensive 2 TB DRAM. Since the number of compute cores that can connect to shared DRAM with independent high-bandwidth channels is limited (e.g., up to 24 cores), this arrangement limits the number of independent compute threads (e.g., up to 128 compute threads) that can be used for de novo sequencing.

For referenced-aligned sequencing, which uses a reference genome to locate sample reads within a sample genome, the full reference genome is typically searched for each sample read to locate the sample read within the reference genome. Such reference-aligned sequencing also requires significant memory resources to store the full reference genome and a high computational cost to compare each sample read to the full reference genome. Conventional methods of referenced-aligned sequencing also have limited scalability. In more detail, conventional methods of referenced-aligned sequencing may randomly partition the sample reads into groups that are processed by a corresponding compute thread. However, each compute thread typically needs a large dedicated memory, such as a 16 GB DRAM, to store the entire reference genome. In other techniques, the reference genome may be stored in a single shared 16 GB DRAM, but as noted above for conventional de novo sequencing, this shared memory arrangement limits the number of cores and compute threads that can access the shared memory. Accordingly, there is a need to improve genome sequencing in terms of computational cost, memory resources, and scalability.

BRIEF DESCRIPTION OF THE DRAWINGS

The features and advantages of the embodiments of the present disclosure will become more apparent from the detailed description set forth below when taken in conjunction with the drawings. The drawings and the associated descriptions are provided to illustrate embodiments of the disclosure and not to limit the scope of what is claimed.

FIG. **1** is a block diagram of a system for genome sequencing including a reference-guided device according to one or more embodiments.

FIG. **2** illustrates an example of a plurality of groups of cells in a reference-guided device according to one or more embodiments.

FIG. **3** is a graph depicting the uniqueness of substrings of different lengths in human reference genome H38.

FIG. **4**A illustrates an example of identifying groups of cells in a reference-guided device where a stored current substring sequence matches a reference sequence according to one or more embodiments.

FIG. **4**B is an example of circuitry for comparing a substring base value to a reference base value stored in a cell according to one or more embodiments.

FIG. **4**C is an example of circuitry for comparing cell output values in a group of cells according to one or more embodiments.

FIG. **5** is a flowchart for a sample read location process according to one or more embodiments.

FIG. **6** is a flowchart for a match identification subprocess using logical operations according to one or more embodiments.

FIG. **7** is a flowchart for a match identification subprocess using inner-products of reference vectors and substring vectors according to one or more embodiments.

DETAILED DESCRIPTION

In the following detailed description, numerous specific details are set forth to provide a full understanding of the present disclosure. It will be apparent, however, to one of ordinary skill in the art that the various embodiments disclosed may be practiced without some of these specific details. In other instances, well-known structures and techniques have not been shown in detail to avoid unnecessarily obscuring the various embodiments.

System Examples

FIG. **1** is a block diagram of system **100** for genome sequencing including host **101** and reference-guided device **102** according to one or more embodiments. Host **101** communicates with reference-guided device **102** to determine a probabilistic location of a sample read within a reference genome. In some implementations, device **102** can provide host **101** with index 10 stored in memory **108** of device **102** indicating a probabilistic location of the sample read. In other implementations, device **102** may provide host **101** with another data structure or indication of the probabilistic location of the sample read.

The sample reads, or sample substring sequences taken from the sample reads, may initially be provided to reference-guided device **102** by host **101** and/or by another device not shown in FIG. **1**, such as by additional hosts, to determine probabilistic locations of the sample reads within a reference genome stored in one or more arrays **104** of device **102**. In some implementations, a read device that generates the sample reads, such as an Illumina device (from Illumina, Inc. of San Diego, California) or a nanopore device may provide sample reads to reference-guided device **102**.

For ease of description, the example embodiments in this disclosure will be described in the context of DNA sequencing. However, the embodiments of the present disclosure are not limited to DNA sequencing, and can be generally applied to any nucleic acid-based sequencing including RNA (ribonucleic acid) sequencing.

Host **101** can include, for example, a computer such as a desktop or server that may implement genome sequencing algorithms, such as a seed and extend algorithm for exact matching and/or a more computationally complex algorithm, such as a Burrows-Wheeler algorithm or Smith-Waterman algorithm for approximate matching of sample reads in a genome. As discussed in more detail below, device **102** may be used to preprocess sample reads before de novo or referenced-aligned sequencing. In this regard, the probabilistic locations provided by reference-guided device **102** may replace or improve the efficiency of algorithms performed by host **101** in terms of memory resources and computational cost. In addition, and as described in related co-pending application Ser. Nos. 16/821,849, and 16/822,010, both of which are incorporated by reference above, the probabilistic locations of sample reads provided by device **102** can allow for improvements to the scalability of genome sequencing, thereby lowering the expense and time to perform de novo or reference-aligned genome sequencing.

Reference-guided device **102** in some implementations can include, for example, one or more Application Specific Integrated Circuits (ASICs) or Field Programmable Gate Arrays (FPGAs) for generating index 10 indicating the probabilistic locations of sample substring sequences from a sample read relative to a reference genome. The probabilistic locations of the sample substring sequences can provide host **101** with a probabilistic location for the sample read from which the sample substring sequences were taken. In some implementations, host **101** or another device may provide reference-guided device **102** with a current sample substring sequence to load into the one or more arrays **104** of device **102**. In other implementations, host **101** or another device may provide reference-guided device **102** with a sample read and reference-guided device **102** may determine the sample substring sequences from the sample read to be loaded into the one or more arrays **104**.

Host **101** and device **102** may or may not be physically co-located. For example, in some implementations, host **101** and device **102** may communicate via a network, such as by using a Local Area Network (LAN) or Wide Area Network (WAN), such as the internet, or a data bus or fabric. In addition, those of ordinary skill in the art will appreciate that other implementations may include multiple hosts **101** and/or multiple devices **102** for providing probabilistic locations of sample reads. In certain embodiments, host **101** and device **102** (or multiple hosts and devices) are integrated as a single device or system.

As shown in the example of FIG. **1**, device **102** includes one or more arrays **104**. As used herein, a cell generally refers to a memory location for storing one or more values representing one or more nucleotides, referred to as bases in the present disclosure. In some implementations, array or arrays **104** can include cells that also include logic for performing one or more operations on a value or values stored in the cell. In such examples, each cell in the one or more arrays can store a reference value representing a reference base from a reference genome and a sample value representing a base from a sample substring sequence. The cell may perform one or more operations to output a value that can be used by circuitry **106** or circuitry of the one or more arrays **104** to determine whether a group of cells in the one or more arrays **104** stores a reference sequence that matches the substring sequence stored in the group of cells. In some implementations, array(s) **104** can include one or more systolic arrays where a reference value representing a reference base from the reference genome is loaded, and a sample value representing a base from a sample substring sequence may be loaded into the cell for comparison to the reference value, before passing the sample value to a next cell in another group of cells of array(s) **104**.

In other implementations, array or arrays **104** can include solid-state memory cells that may not perform operations to determine if the values stored in the cell match. For example, circuitry **106** in some implementations may determine if the values stored in each cell match. As another variation, array or arrays **104** may each store either a reference value representing a reference base or a sample value representing sample base. In such an implementation, cells storing reference values may be paired with cells storing sample values for comparison of the reference bases to the sample bases. In yet other implementations, the cells in array(s) **104** can include circuitry elements such as registers, latches, or flip-flops.

While the description herein refers to solid-state memory generally, it is understood that solid-state memory may comprise one or more of various types of memory devices such as flash integrated circuits, Chalcogenide RAM (C-RAM), Phase Change Memory (PC-RAM or PRAM), Programmable Metallization Cell RAM (PMC-RAM or PMCm), Ovonic Unified Memory (OUM), Resistive RAM (RRAM), NAND memory (e.g., Single-Level Cell (SLC) memory, Multi-Level Cell (MLC) memory (i.e., two or more levels), or any combination thereof), NOR memory, Electrically Erasable Programmable Read-Only Memory (EEPROM) EEP-OM, Ferroelectric Memory (FeRAM), Magnetoresistive RAM (MRAM), other discrete Non-Volatile Memory (NVM) chips, or any combination thereof.

Circuitry **106** can include, for example, hard-wired logic, analog circuitry and/or a combination thereof. In other implementations, circuitry **106** can include one or more ASICs, microcontrollers, Digital Signal Processors (DSPs), FPGAs, and/or a combination thereof. In some implementations, circuitry **106** can include one or more Systems on a Chip (SoCs), which may be combined with memory **108**. As discussed in more detail below, circuitry **106** is configured to identify groups of cells in array or arrays **104** where a stored reference sequence matches a current substring sequence stored in the group of cells.

In more detail, for each group of cells in array or arrays **104**, a reference sequence for reference bases from a reference genome can be stored in the group of cells. The reference sequence corresponds to an order of the cells in the respective group of cells. Each group of cells is configured to store a reference sequence representing a portion of a reference genome that partially overlaps at least one other portion of the reference genome represented by one or more other reference sequences stored in one or more other groups of cells. An example of the storage of such overlapping reference sequences in an array is discussed in more detail below with reference to FIG. **2**.

In addition, each group of cells in array or arrays **104** is configured to store the same current substring sequence that corresponds to the order of the respective group of cells. As noted above, circuitry **106** is configured to identify groups of cells among the plurality of groups of cells in array or arrays **104** where the stored current substring sequence matches the reference sequence stored in the groups of cells. The identification of groups of cells with matching sequences may be made in some implementations by circuitry **106** based on values output from the cells after performing at least one logical operation, such as an XNOR operation. In other implementations, the identification of groups of cells with matching sequences may be made by circuitry **106** based on values output from the cells after multiplying a reference value representing the reference base and a sample value representing the sample base. In yet other implementations, circuitry **106** may perform all of the operations on the values stored in the cells, instead of some of the operations being performed by the cells themselves.

Memory **108** of device **102** can include, for example, a volatile memory, such as Dynamic Random Access Memory (DRAM), for storing index 10. In other implementations, memory **108** can include a nonvolatile memory, such as MRAM. As shown in FIG. **1**, memory **108** stores index 10, which can be used by host **101** to determine a probabilistic location of a sample read within the reference genome represented by the overlapping reference sequences loaded into or stored in array or arrays **104**. In some implementations, index 10 can include a data structure, such as a bitmap or other data structure indicating an index or position in the reference genome corresponding to the groups of cells identified as storing matching sequences. Circuitry **106** may update index 10 for different sample substring sequences that are loaded into each group of cells of array or arrays **104**. In some implementations, circuitry **106** may indicate a mean location in index 10 for a substring sequence that has multiple matching groups of cells. In other implementations, only a first matching group of cells for a particular substring sequence may be used, or circuitry **106** may not update index 10 at all for a substring sequence that has more than a single group of cells storing matching sequences.

In addition, some implementations may not use an index or other data structure for indicating the location of groups of cells with matching sequences. For example, circuitry **106** in some implementations may output data directly to host **101** indicating groups of cells with matching sequences.

As will be appreciated by those of ordinary skill in the art with reference to the present disclosure, other implementations may include a different number or arrangement of components than shown for system **100** in the example of FIG. **1**. For example, other implementations may combine host **101** and device **102** or may include a different number of devices **102** and/or hosts **101**.

FIG. **2** illustrates an example of a plurality of groups of cells in reference-guided device **102** according to one or more embodiments. As shown in the example of FIG. **2**, array **104** includes groups of cells $\mathbf{110}_1$ to $\mathbf{110}_{L-19}$. Although groups of cells $\mathbf{110}_1$ to $\mathbf{110}_{L-19}$ in FIG. **2** are shown as columns, other implementations may include groups of cells that are not physically arranged as columns. In some implementations, array **104** may substitute a defective cell from one group of cells with another cell located in a pool of spare cells in a different portion of the same array or in a different array. In implementations where each group of cells stores an overlapped reference sequence that has been shifted by one reference base from the previous group of cells, L can equal the full length of the reference genome, such as 3.2 billion groups or columns of cells, as in the case of the full reference human genome H38. Other implementations may instead store overlapped reference sequences that have been shifted by a different number of reference bases, such as by two reference bases, so that fewer groups of cells or columns are needed, which allows for a smaller size of array **104**. However, shifting the overlap by more than one reference base can come at a cost of reducing the likelihood of finding matches for the substring sequence.

As shown in the example of FIG. **2**, each group of cells **110** stores a reference value (e.g., R1, R2, R3, etc.) representing a reference base and a sample value (S1, S2, S3, etc.) representing a sample base. Each reference value and each sample value can be represented by two bits, since there are four possible bases—Adenine (A), Guanine (G), Cytosine (C), and Thymine (T), in the case of DNA sequencing, for example. While each group of cells **110** stores the same sample sequence of sample values S1 to S20, each group of cells **110** stores different partially overlapping reference sequences that are shifted by one reference base from a reference sequence stored in an adjacent group of cells. For example, group of cells $\mathbf{110}_1$ stores a first reference sequence with reference values R1 to R20, and group of cells $\mathbf{110}_2$ stores a second reference sequence with reference values R2 to R21. In other embodiments, the shifted-by offsets and resulting overlaps may be different across the cell groups than as shown in the example of FIG. **2**.

The arrangement of storing partially overlapping reference sequences and substring sequences in array **104** ordinarily allows for an efficient locating of a probabilistic location of a sample read within the reference genome. In addition, the reference sequences only need to be loaded into or stored a single time in array **104**. Iterations of loading or storing different substring sequences from a sample read may then provide a probabilistic location of the sample read within the reference genome, which may be used by host **101** to intelligently sort sample reads into groups of reads for more efficient de novo or reference-aligned sequencing, as discussed in co-pending related application Ser. No. 16/821,849, and 16/822,010, incorporated by reference above. In this regard, different implementations may use a first type of cell, such as a ROM or NAND flash cell, to store the reference sequences, and a second type of cell that is better suited to repeated overwrites with a better write endurance, such as an MRAM cell, to store substring sequences.

A substring sequence length of 20 is used in the example of FIG. **2** including sample values S1 to S20. As discussed in more detail below with reference to FIG. **3**, the length of the substring sequence, which corresponds to the number of cells in a group of cells or column, can be selected based on a desired uniqueness of the substring sequences within the reference genome relative to the number of cells and operations needed to identify groups of cells or columns storing matching sequences.

FIG. **3** is a graph depicting the uniqueness of substring sequences of different lengths in human reference genome H38. The dashed line in FIG. **3** represents an expected profile if each base in reference genome H38 is chosen uniformly at random for the different substring lengths indicated along the x-axis. The solid line in FIG. **3** represents an observed uniqueness of substring sequences within reference genome H38 for the different substring lengths indicated along the x-axis. Specifically, 1,000 substring sequences having lengths between 1 and 44 bases were chosen randomly, and for each substring sequence, the number of matches in H38 were counted. The difference between the solid line and the dashed line in FIG. **3** shows that the distribution of bases in the reference genome is not entirely random. As a result, a slightly longer substring length can be used in practice than in the uniformly random profile to obtain more unique matches.

As shown by the solid line in FIG. **3**, substring sequences with lengths between 17 and 25 bases can provide a sufficient number of unique matches for most substring sequences (i.e., only matching at one location within H38) for locating the substring sequence within H38. A substring length shorter than 17 bases will require a greater number of substring sequences from a sample read to determine the probabilistic location of the sample read within the reference genome. As shown in FIG. **3**, a substring length shorter than 15 bases, may fail to identify any unique matches within H38 for nearly all the substring sequences attempted.

On the other hand, a substring length greater than 25 bases, would incur additional storage cost in terms of cells in array or arrays **104** and a greater computational cost due to the increase in operations needed, with little improvement in the number of unique matches. As a result, the example of FIG. **2** discussed above uses a substring length of 20 bases, which means that each group of cells **110** in FIG. **2** includes a predetermined number of 20 cells. Those of ordinary skill in the art will appreciate with reference to the present disclosure that a different substring length or a different predetermined number of cells in each group of cells may be preferred for other examples, such as when using a different reference genome or a portion of reference genome, as may be the case for medical diagnosis of a genetic condition related to a particular portion of a reference genome. In addition, different tradeoffs between computational cost, the number of cells, and accuracy in terms of a greater number of unique matches may also affect the number of cells used for each group of cells in array or arrays **104**.

FIG. **4**A illustrates an example array for identifying groups of cells where a stored current substring sequence matches a reference sequence according to one or more embodiments. As shown in FIG. **4**A, array **104** includes a plurality of groups of cells, as with the example of FIG. **2** discussed above. In the example of FIG. **4**A, each group of cells is represented by a column number i, from 1 to L-(M−1). Each cell within each group of cells, or column, is also represented by a row number j, from 1 to M. As discussed above, L-(M−1) can correspond to the number of overlapping reference sequences from a reference genome, and M can correspond to a number of bases in a substring sequence, such as 20 bases, as with the example array **104** in FIG. **2**.

Reference sequences for the reference genome can be loaded or stored in the groups of cells with each cell storing a reference value representing a reference base from the reference sequence. As discussed above, the reference sequences from one column or group of cells to the next group or column may overlap by a predetermined number of reference values or reference bases, such as by one, two or three reference values or bases. The order of cells in the group or column corresponds to the order of reference bases in the reference sequence. In some implementations, the reference sequences may be initially loaded or stored by a manufacturer of the reference-guided device for a particular reference genome before shipping the reference-guided device to a customer. In other implementations, the reference sequences may be loaded or stored by the customer in the field.

A current substring sequence is loaded or stored in the groups of cells with each cell storing a sample value representing a sample base from the current substring sequence. Each group of cells or column can store the same current substring sequence. In addition, the order of cells in the group or column corresponds to the order of sample bases in the current substring sequence. In some implementations, array **104** can include a systolic array where the current substring sequence is passed from one group of cells or column to the next.

As discussed in more detail below with reference to FIGS. **4**B and **4**C, a comparison is made between the reference value and the sample value in each cell, such as in cell i, j, and each cell provides a cell output value to circuitry **106** to identify columns or groups of cells where all of the reference values match all of the substring values. The position of the matching columns or groups of cells may then be used to update a data structure, such as index 10 in FIG. **1**. In other implementations, the position of the matching columns or groups of cells may instead be provided to another device, such as host **101** in FIG. **1**, without updating a data structure.

FIG. **4**B is an example of circuitry for comparing a substring base value to a reference base value stored in a cell according to one or more embodiments. As noted above, each substring base and reference base can be represented by two bits. For example, an A base can be represented by the binary value 00, a C base can be represented by the binary value 01, a G base can be represented by the binary value 10, and a T base can be represented by the binary value 11. In other implementations, the bases can be represented by other values, as in the example of using inner-products discussed below with reference to FIG. **7** where bases can have values including 1 or −1.

As shown in the example of FIG. **4**B, circuitry within cell i,j includes two XNOR gates that output to an AND gate. In more detail, a first bit of substring base value i,j stored in cell i,j is input into a first XNOR gate together with a first bit of reference base value i,j stored in cell i,j. A second bit of substring base value i, j is input into a second XNOR gate together with a second bit of reference base value i, j. If the two inputs of an XNOR gate match, the output has a high binary value of 1. On the other hand, if the two inputs of an XNOR gate do not match, the output has a low binary value of 0.

The output value from each XNOR gate is input into the AND gate. If the two inputs are both 1, indicating a match for each of the first and second bits of the reference base value and substring base value, the cell comparison output value from the AND gate is a high binary value of 1. Otherwise, the cell comparison output value from the AND gate is a low binary value of 0. This high or low binary value is output from the cell to circuitry, such as to circuitry **106** in FIG. **1**, to identify columns or groups of cells where all of the reference base values match all of the substring base values stored in the group of cells.

FIG. **4**C is an example of circuitry for comparing cell output values in a group of cells according to one or more embodiments. As shown in FIG. **4**C, the cell comparison output values from each cell in a group of cells are input into an AND gate to produce a column output value for column i. If the cell comparison output values for all the cells **1** to M in column i indicate a match by all having high binary values of 1, the column output value from the AND gate for the column is a high binary value of 1. This column output value may be used to identify the column or group of cells as having a matching substring sequence and reference sequence. The circuitry shown in FIG. **4**C may be part of circuitry external to the array **104** or may be part of the array **104**.

In some cases, there may be multiple groups of cells identified as storing a reference sequence that matches the current substring sequence. In such cases, circuitry **106** may only use the first matching location, the first matching location with other matching locations, or may use all of the matching locations for locating the current substring sequence within the reference genome. In other cases, the current substring sequence may result in no matches. For example, mutations or read errors in the sample read from which the substring sequence is taken may prevent a match or may cause errors in the matching.

Other implementations may use different circuitry or a different process of identifying groups of cells where the stored reference sequence matches a substring sequence stored in the group of cells. For example, an inner-product or dot product operation may instead be used to identify groups of cells storing matching sequences, instead of logic gates, as discussed in more detail below with reference to the match identification sub-process of FIG. **7**. As another example, the AND gate in FIG. **4**C may be replaced by circuitry for summing the cell comparison output values for a group of cells and then comparing the sum to the number of cells in the group of cells. In such an example, the reference sequence for the group of cells matches the substring sequence if the sum from the cells in the group equals the number of cells in the group.

Example Identification Processes

FIG. **5** is a flowchart for a sample read location process according to one or more embodiments. The process of FIG. **5** may be performed, for example, by device **102** and/or host **101** in FIG. **1**.

In block **502**, reference sequences are stored in respective groups of cells of a plurality of groups of cells for reference bases from a reference genome. As noted above with reference to FIG. **2**, the storage locations of the reference sequences correspond to an order of cells in the groups of cells. In addition, each reference sequence represents a portion of the reference genome that partially overlaps or is shifted from at least one other portion of the reference genome represented by one or more other reference sequences stored in one or more other groups of cells.

In some implementations, reference-guided device **102** may receive the reference sequences or the reference genome from host **101**. In other implementations, reference-guided device **102** may come pre-configured from the manufacturer with the reference sequences programmed or stored in the groups of cells for a particular genome, such as human genome H38.

In block **504**, the current substring sequence is stored in each group of cells of the plurality of groups of cells for sample bases from a sample read. The storage locations of the current substring sequence within each group of cells corresponds to an order of the group of cells. The current substring sequence may be received from host **101** or may be selected by device **102** from a sample read provided by host **101**. In some implementations, circuitry **106** of device **102** or host **101** may randomly select substring sequences from the sample read. In other implementations, circuitry **106** or host **101** may select substring sequences that are spaced throughout the sample read.

In block **506**, circuitry **106** identifies groups of cells among the plurality of groups of cells where the stored reference sequence matches the current substring sequence stored in the group of cells. In some implementations, the identification of groups of cells may be made using logic gates, as in the examples discussed above for FIGS. **4**A to **4**C. In other implementations, the identification of groups of cells may be made by performing calculations using the stored reference values and sample values, as with the example match identification sub-process of FIG. **7** discussed below.

In block **508**, circuitry **106** or host **101** determines whether the substring sequence stored in block **504** is the last substring sequence from the sample read to be stored in the groups of cells. In some implementations, a predetermined number of substring sequences may be iteratively stored in cells of device **102** for comparison to reference sequences from the reference genome. The number of different substring sequences taken from a sample read can depend on, for example, the length of the substring sequences (e.g., 20 bases in FIG. **2**), the length of the reference genome, the length of the sample read (e.g., a short read from an Illumina device of 250 or 300 bases versus a long read from a nanopore device of 5,000 bases), an accuracy of the process used to create the sample read, and a desired accuracy for locating the sample read within the reference genome. In one example, short reads of 250 or 300 bases can be located in a reference genome with only a few matching substring sequences. Such an example may only use ten substring sequences from sample reads to generate enough matches to locate the sample reads in the reference genome.

If it is determined in block **508** that the current substring sequence is not the last substring sequence from the sample read, the process proceeds to block **510** to overwrite the current substring sequence with a next substring sequence from the sample read to store the next substring sequence in the plurality of groups of cells. The process of FIG. **5** then returns back to block **506** to identify groups of cells where the reference sequence matches the next substring sequence. Notably, block **502** is not repeated, since the same reference sequences can be reused for the next substring sequence. Only having to load or store the reference sequences or reference genome a single time for multiple iterations of substring sequences from sample reads can improve the efficiency of the sample read location identification process.

In some implementations, circuitry **106** or host **101** may determine in block **508** whether another substring sequence is needed to locate the sample read based on a number of previously tested substring sequences. For example, if four previous substring sequences have resulted in matches, a fifth substring sequence may not need to be tested. On the other hand, if the four previous substring sequences have not resulted in any matches, a fifth substring sequence can be loaded.

If it is determined in block **508** that the current substring sequence is the last substring sequence from the sample read, the process proceeds to block **512** to determine a probabilistic location of the sample read within the reference genome based on the identified groups of cells for different substring sequences from the sample read. As noted above for block **506**, a first matching group of cells may be used as a location for each substring sequence, or alternatively, multiple matching groups of cells may be used as possible locations for the substring sequence, assuming some substring sequences result in multiple matching groups of cells. In other cases, a substring sequence may have no matching locations due to errors in reading the sample or mutations in the sample. The location for the sample read determined in block **512** by circuitry **106** or host **101** can be probabilistic in the sense that multiple possible locations can be identified for the different substring sequences from the sample read, and a consensus or statistic derived from the matching locations can be used to probabilistically locate the sample read within the reference genome.

In one example, a mean of all the locations of all of the matching groups of cells for all the substring sequences is used to identify a most likely location of the sample read within the reference genome. In another example, only one location for each substring sequence with a matching group of cells is used in the mean. In yet another example, a probabilistic location of the sample read may be determined by identifying the farthest apart locations within the reference genome that correspond to matching groups of cells for the substring sequences. In other examples, one or more outlier locations with respect to a group of matching locations may be discarded in determining the probabilistic location of the sample read within the reference genome.

FIG. **6** is a flowchart for a match identification sub-process using logical operations according to one or more embodiments. The sub-process of FIG. **6** may be performed by cells in array(s) **104** and/or circuitry **106** as part of block **506** in the sample read location process of FIG. **5** discussed above to identify groups of cells where stored reference sequences match a current substring sequence stored in the group of cells.

In block **602**, at least one XNOR operation is performed in each cell of the plurality of groups of cells to compare a sample base from a current substring sequence with a reference base from a reference sequence. As discussed above with reference to FIG. **4**A, two XNOR gates and an AND gate may be used in the cells to compare the values stored in the cell for the reference base and the sample base.

In block **604**, a comparison value is output from each cell of the plurality of groups of cells indicating whether the sample base for the cell matches the reference base for the cell. The comparison value may be either a high binary value of 1 or a low binary value of 0 indicating whether the reference value and the sample value stored in the cell match.

In block **606**, circuitry **106** identifies groups of cells where the stored reference sequence matches the current substring sequence by performing an AND operation on the comparison values output from the cells in respective groups of cells. If any of the comparison values have a low binary value of 0, the result of the AND operation will have a low binary value of 0, indicating that the group of cells does not store matching sequences. On the other hand, if all of the comparison values have a high binary value of 1, the result of the AND operation will have a high binary value of 1, indicating that the group of cells stores matching sequences. In other implementations, circuitry **106** may identify groups of cells where the stored reference sequence matches the current substring sequence by summing the comparison values and comparing the sum to a predetermined number of cells in the group of cells. In such implementations, if all of the comparison values from the cells have a value of 1, the sum of the comparison values for the group of cells will equal the total number of cells in the group of cells when all of the cells have matching values. Although XNOR and AND are mentioned as examples, those of ordinary skill in the art will recognize that the same result can be achieved in other embodiments through other logic combinations.

As noted above, other processes may be used to identify groups of cells where the stored reference sequence matches a substring sequence stored in the group of cells. In this regard, FIG. **7** is a flowchart for a match identification sub-process that uses inner-products or dot products of reference vectors and substring vectors according to one or more embodiments. The sub-process of FIG. **7** may be performed by cells in array(s) **104** and/or circuitry **106** as part of block **506** in the sample read location process of FIG. **5** discussed above to identify groups of cells where stored reference sequences match a current substring sequence stored in the group of cells.

In block **702**, a product is calculated for each cell of a first stored value representing a substring base and a second stored value representing a reference base. The substring values stored in a group of cells can represent a substring vector, and the reference values stored in the group of cells can represent a reference vector for the group of cells. For example, each reference value and each sample value can be represented by two digits including 1 and/or −1. In such an example, the base C may have a value of 1,1, the base G may have a value of −1,−1, the base T may have a value of 1,−1, and the base A may have a value of −1,1. As will be appreciated by those of ordinary skill in the art with reference to the present disclosure, different combinations of 1 and −1 may be used to represent the bases.

In block **704**, the calculated product for each cell in a group of cells is output from each cell to circuitry **106**. In other implementations, circuitry **106** may calculate the product of the values stored in the cells.

For each group of cells, the products output from the cells are summed in block **706**. The sum of the products for each group of cells is then compared in block **708** to twice the number of cells in the group of cells or twice the length of the substring sequence. In other implementations, the sum of the products for each group of cells may be compared to a different predetermined multiple of the number of cells in the group. For example, in an implementation where the cells output a value of 1 indicating a match and a value of 0 indicating no match, the sum is compared to 1 multiplied by the total number of cells, rather than twice the number of cells in the group. Similarly, in an implementation where the cells output a value of 0 indicating a match, the sum is compared to 0 multiplied by the number of cells.

In block **710**, circuitry **106** or host **101** identifies groups of cells where the sum of the products equals twice the number of cells in the group of cells or twice the length of the substring sequence. Such groups of cells have matching sequences because each product from the cells for such groups equal 1, and therefore add up to twice the number of cells (or twice the substring sequence length).

For example, using only four bases for a substring sequence length, which is shorter for purposes of illustration than the range of 17 to 25 bases discussed above, a reference sequence for a group of cells can be represented as R=CCAG, a matching substring sequence can be represented as S1=CCAG, and a non-matching substring sequence can be represented as S2=GGAG. The encoded reference sequence or reference vector is then [1,1,1,1,−1, 1,−1,−1] using the values assigned to the bases discussed above for block **702**. The encoded matching substring sequence or matching substring sequence vector would also be [1,1,1,1,−1,1,−1,−1]. The encoded non-matching substring sequence or non-matching substring sequence vector would be [−1,−1,−1,−1,−1, 1,−1].

Taking the dot product or inner-product of the reference vector and the matching substring sequence vector results in 8, which is twice the number of cells in the group of cells or twice the length of the substring sequence length of 4 bases. On the other hand, taking the dot product or inner-product of the reference vector and the non-matching substring sequence vector results in 0, which is less than twice the number of cells in the group or the length of the substring sequence. Accordingly, inner-products or dot products that result in values less than twice the number of cells in the group or twice the length of the substring sequence do not correspond to groups of cells storing matching sequences.

As discussed above, the foregoing reference-guided devices and methods can ordinarily allow sample reads to be probabilistically located within a reference genome. This can improve the efficiency of de novo and reference-aligned sequencing by pre-processing sample reads into groups based on their locations in the reference genome for further sequencing. In the case of de novo sequencing, this can improve the scalability and efficiency of de novo sequencing by allowing more compute threads to access each localized group of sample reads in a smaller shared memory, as compared to conventional methods where a larger and more expensive memory is used to access all of the sample reads by a limited number of compute threads. In the case of reference-aligned sequencing, the localized groups of sample reads can allow for only a smaller relevant portion of a reference genome to be stored in a smaller and less expensive memory for each localized group, while allowing for more compute threads to access the multiple smaller memories to improve scalability, as compared to a conventional reference-aligned sequencing that may use a single shared memory to store the full reference genome.

Other Embodiments

Those of ordinary skill in the art will appreciate that the various illustrative logical blocks, modules, and processes described in connection with the examples disclosed herein may be implemented as electronic hardware, software, or combinations of both. Furthermore, the foregoing processes can be embodied on a computer readable medium which causes a processor, controller, or other circuitry to perform or execute certain functions.

To clearly illustrate this interchangeability of hardware and software, various illustrative components, blocks, and modules have been described above generally in terms of their functionality. Whether such functionality is implemented as hardware or software depends upon the particular application and design constraints imposed on the overall system. Those of ordinary skill in the art may implement the described functionality in varying ways for each particular application, but such implementation decisions should not be interpreted as causing a departure from the scope of the present disclosure.

The various illustrative logical blocks, units, modules, and circuitry described in connection with the examples disclosed herein may be implemented or performed with a general purpose processor, a GPU, a DSP, an ASIC, an FPGA or other programmable logic device, discrete gate or transistor logic, discrete hardware components, or any combination thereof designed to perform the functions described herein. A general purpose processor may be a microprocessor, but in the alternative, the processor may be any conventional processor, controller, microcontroller, or state machine. Processor or controller circuitry may also be implemented as a combination of computing devices, e.g., a combination of a DSP and a microprocessor, a plurality of microprocessors, an SoC, one or more microprocessors in conjunction with a DSP core, or any other such configuration.

The activities of a method or process described in connection with the examples disclosed herein may be embodied directly in hardware, in a software module executed by processor or controller circuitry, or in a combination of the two. The steps of the method or algorithm may also be performed in an alternate order from those provided in the examples. A software module may reside in RAM memory, flash memory, ROM memory, EPROM memory, EEPROM memory, registers, hard disk, a removable media, an optical media, or any other form of storage medium known in the art. An exemplary storage medium is coupled to processor or controller circuitry such that the processor or controller circuitry can read information from, and write information to, the storage medium. In the alternative, the storage medium may be integral to processor or controller circuitry. The processor or controller circuitry and the storage medium may reside in an ASIC or an SoC.

The foregoing description of the disclosed example embodiments is provided to enable any person of ordinary skill in the art to make or use the embodiments in the present disclosure. Various modifications to these examples will be readily apparent to those of ordinary skill in the art, and the principles disclosed herein may be applied to other examples without departing from the spirit or scope of the present disclosure. The described embodiments are to be considered in all respects only as illustrative and not restrictive. In addition, the use of language in the form of "at least one of A and B" in the following claims should be understood to mean "only A, only B, or both A and B."

What is claimed is:

1. A device, comprising:

at least one two-dimensional systolic array including a plurality of groups of cells, wherein each group of cells of the plurality of groups of cells is configured to:

store a reference sequence representing reference bases from a reference genome, the reference sequence corresponding to an order of cells in the respective group of cells; and

store a current substring sequence representing sample bases from a sample read by passing the current substring sequence from one group of cells to a next group of cells in the at least one two-dimensional systolic array with the current substring sequence corresponding to the order of the cells in the respective group of cells;

wherein each group of cells of the plurality of groups of cells is further configured to store the same current substring sequence and a reference sequence representing a portion of the reference genome that partially overlaps at least one other portion of the reference genome represented by one or more other reference sequences stored in one or more other groups of cells of the at least one two-dimensional systolic array; and

circuitry configured to identify groups of cells in the at least one two-dimensional systolic array where the stored reference sequence matches the current substring sequence stored in the group of cells.

2. The device of claim **1**, wherein at least one of the circuitry and each group of cells are further configured to perform one or more logic operations to determine whether the stored reference sequence matches the current substring sequence stored in the group of cells.

3. The device of claim **1**, wherein each cell of the plurality of groups of cells is further configured to:

perform at least one XNOR operation to compare a first value stored in the cell for a sample base from the current substring sequence with a second value stored in the cell for a reference base from the reference sequence stored in the respective group of cells; and

output a comparison value to the circuitry for the at least one XNOR operation indicating whether the sample base for the cell matches the reference base for the cell.

4. The device of claim **3**, wherein the circuitry is further configured to identify groups of cells where the stored reference sequence matches the current substring sequence stored in the group of cells by performing an AND operation on the comparison values output from the cells for respective groups of cells.

5. The device of claim **1**, wherein each cell of the plurality of groups of cells is further configured to:

calculate a product of values stored in the cell representing the sample base and the reference base; and

output the product to the circuitry; and

wherein the circuitry is further configured to identify groups of cells where the stored reference sequence matches the current substring sequence stored in the group of cells based at least in part on the products output by the cells.

6. The device of claim **5**, wherein the circuitry is further configured to, for each group of cells of the plurality of groups of cells:

sum the products output by the cells in the group of cells;

compare the sum to a predetermined multiple of the number of cells in the group of cells; and

in response to the sum being equal to the predetermined multiple of the number of cells in the group of cells, identify the group of cells as where the stored reference sequence matches the current substring sequence stored in the group of cells.

7. The device of claim **1**, wherein each group of cells in the plurality of groups of cells consists of a predetermined number of cells, the predetermined number of cells being within a range of 17 to 25 cells.

8. The device of claim **1**, wherein each group of cells of the plurality of cells is further configured to:

overwrite the current substring sequence with a subsequent substring sequence representing sample bases from the sample read to store the subsequent substring sequence in the group of cells; and

retain the respective reference sequence stored in the group of cells; and

wherein the circuitry is further configured to identify groups of cells among the plurality of groups of cells where the retained reference sequence stored in the group of cells matches the subsequent substring sequence stored in the group of cells.

9. The device of claim **1**, wherein the circuitry is further configured to determine a probabilistic location of the sample read within the reference genome based on iterations of:

storing different substring sequences for the sample read in the plurality of groups of cells; and

identifying groups of cells among the plurality of groups of cells where the stored reference sequence matches the substring sequence stored in the group of cells.

10. The device of claim **1**, wherein the circuitry includes at least one of a Field Programmable Gate Array (FPGA) and an Application Specific Integrated Circuit (ASIC).

11. The device of claim **1**, wherein the cells in the plurality of groups of cells comprise at least one of registers, latches, and flip-flops.

12. A method of locating a sample read with respect to a reference genome, the method comprising:

storing, in a plurality of groups of cells of at least one two-dimensional systolic array, reference sequences representing reference bases from the reference genome, the reference sequences corresponding to an order of cells in respective groups of cells of the plurality of groups of cells, wherein each group of cells of the plurality of groups of cells stores a reference sequence representing a portion of the reference genome that partially overlaps at least one other portion of the reference genome represented by one or more other reference sequences stored in one or more other groups of cells;

storing, in each group of cells of the plurality of groups of cells, a current substring sequence for sample bases from the sample read by passing the first substring sequence from one group of cells to a next group of cells in the at least one two-dimensional systolic array with the current substring sequence corresponding to the order of cells in the respective groups of cells; and

identifying groups of cells in the at least one two-dimensional systolic array where the stored reference sequence matches the current substring sequence stored in the group of cells.

13. The method of claim **12**, further comprising performing one or more logic operations for each group of cells to determine whether the stored reference sequence matches the current substring sequence stored in the group of cells.

14. The method of claim **12**, further comprising, for each cell of the plurality of groups of cells:

performing at least one XNOR operation for a first value stored in the cell for a sample base from the current substring sequence with a second value stored in the cell for a reference base from the reference sequence stored in the respective group of cells; and

outputting a comparison value for the at least one XNOR operation indicating whether the sample base for the cell matches the reference base for the cell.

15. The method of claim **14**, further comprising identifying groups of cells where the stored reference sequence matches the current substring sequence stored in the group of cells by performing an AND operation on the comparison values output from the cells for respective groups of cells.

16. The method of claim **12**, further comprising identifying groups of cells where the stored reference sequence matches the current substring sequence stored in the group of cells by at least, for each group of cells of the plurality of groups of cells, calculating an inner product of a reference vector representing reference bases stored in the group of cells and a substring vector representing sample bases stored in the group of cells.

17. The method of claim **12**, wherein the current substring sequence is within a range of 17 to 25 bases.

18. The method of claim **12**, further comprising, for each group of cells of the plurality of cells:

overwriting the current substring sequence with a subsequent substring sequence of sample bases from the sample read to store the subsequent substring sequence;

retaining the respective portion of the reference genome as the reference sequence stored in the group of cells; and

identifying groups of cells among the plurality of groups of cells where the retained reference sequence stored in the group of cells matches the subsequent substring sequence stored in the group of cells.

19. The method of claim **12**, further comprising determining a probabilistic location of the sample read within the reference genome based on iterations of:

storing different substring sequences from the sample read in the groups of cells of the at least one two-dimensional systolic array; and

identifying groups of cells in the at least one two-dimensional systolic array where the stored reference sequence matches the substring sequence stored in the group of cells.

20. A method of operating a device comprising at least one two-dimensional systolic array including a plurality of groups of cells, the method comprising:

storing, in each group of cells of the plurality of groups of cells, a first substring sequence for sample bases from a sample read by passing the first substring sequence from one group of cells to a next group of cells in the at least one two-dimensional systolic array such that the sample bases in the first substring sequence correspond to the order of cells in the respective groups of cells of the plurality of groups of cells;

wherein each group of cells of the plurality of groups of cells is configured to store a reference sequence representing different portions of a reference genome;

identifying groups of cells in the at least one two-dimensional systolic array where the stored reference sequence matches the first substring sequence stored in the group of cells;

storing, in each group of cells of the plurality of groups of cells, a second substring sequence for sample bases from another portion of the sample read by passing the second substring sequence from one group of cells to a next group of cells in the at least one two-dimensional systolic array such that the sample bases for the second substring sequence correspond to the order of cells in the group of cells and overwrite the first substring sequence; and

identifying groups of cells in the at least one two-dimensional systolic array where the stored reference sequence matches the second substring sequence stored in the group of cells.

21. The method of claim **20**, further comprising, for each of the first substring sequence and the second substring sequence, performing one or more logic operations for each group of cells to determine whether the stored reference sequence matches the substring sequences stored in the group of cells.

22. The method of claim **20**, further comprising performing at least one logical XNOR operation for each cell of the plurality of groups of cells to compare a sample base from the substring sequence stored in the cell with a reference base from the reference sequence stored in the cell; and

outputting a value from each cell of the plurality of groups of cells indicating whether the sample base stored in the cell matches the reference base stored in the cell.

23. The method of claim **22**, further comprising identifying groups of cells where the stored reference sequence matches a substring sequence stored in the group of cells by performing a logical AND operation on the values output from the cells for respective groups of cells.

24. The method of claim **20**, further comprising identifying groups of cells where the stored reference sequence matches a substring sequence stored in the group of cells by at least, for each group of cells of the plurality of groups of cells, calculating an inner product of a reference vector representing reference bases stored in the group of cells and a substring vector representing sample bases stored in the group of cells.

25. The method of claim **20**, further comprising determining a probabilistic location of the sample read within the reference genome based on the identification of at least one of:

one or more groups of cells where the stored reference sequence matches the first substring sequence stored in the one or more groups of cells; and

one or more groups of cells where the stored reference sequence matches the second substring sequence stored in the one or more groups of cells.

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